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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/739,223	12/18/2000	Gerald Batist	701826-05008-CIP	3120

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 06/04/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/739,223	Applicant(s) Batist et al.
	Examiner Shin-Lin Chen	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 23, 2003* .

2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-25* is/are pending in the application.

4a) Of the above, claim(s) *21 and 22* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-20 and 23-25* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Applicants' amendment filed 4-23-03 has been entered. Claims 2-4, 13, 15 and 17-20 have been amended. Claims 1-25 are pending and claims 1-20 and 23-25 are under consideration.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 5 and 7-12 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of killing tumor cells by using a gene construct containing a HSV Tk gene under the control of a rat Hex II promoter *in vitro*, does not reasonably provide enablement for a method of a tumor-selective expression of a gene under the control of a rat Hex II promoter *in vivo* or a method of killing tumor cells by using a gene construct containing a HSV Tk gene or a cytochrome p450 gene and their respective prodrugs under the control of a rat Hex II promoter *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims and is repeated for the reasons set forth in the preceding Official action mailed 12-18-02 (Paper No. 7). Applicant's arguments filed 4-23-03 have been fully considered but they are not persuasive.

Applicants argue that the claimed method is directed to a tumor-selective expression of a gene in a cell not killing tumor cells. Applicants further argue that example I provide increased rat Hex II promoter activity in tumor cells as compared to normal cell and reduction in tumor volume *in vivo*, and *in vitro* data of example II is complementary to *in vivo* data and can substantiate the *in vivo* aspects of the claimed method (amendment, p. 5, 6). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 12-18-02 (Paper No. 7). As discussed in the preceding Official action mailed 12-18-02, the specification states "The invention relates to a novel tumor-specific promoter for use in gene targeted therapy that is differentially regulated in cancer cells, such as to drive a suicide gene in cancer therapy" (see page 1, lines 14-17). The claims read on gene therapy *in vivo* in light of the specification and encompass the use of various vectors such as retrovirus, adenovirus, plasmid, etc. in any kind of mammal including human beings for gene therapy *in vivo* via various administration routes. Tumor selective expression of the rat Hex II promoter activity in cells *in vivo* must have a use and such use is for gene targeted therapy in cancer cells as stated in the specification, i.e. "killing cancer cells". Thus, the claims read on killing tumor cells by using a gene construct containing a HSV Tk gene or a cytochrome p450 gene and their respective prodrugs under the control of a rat Hex II promoter *in vivo*.

The specification fails to provide adequate guidance and evidence that the combination of a toxic gene, such as HSV Tk gene or cytochrome p450 gene, and a prodrug under the control of a rat Hex II promoter would provide sufficient expression of the gene product via various

administration routes such that therapeutic effect, such as inhibiting tumor cell growth or killing tumor cells, can be obtained *in vivo* for a particular cancer cell. Example I of the present invention teaches intratumoral injection of the expression vector expressing Tk protein but fails to provide enabling evidence for tumor-specific activity of the Hex II promoter and reduction in tumor volume via various administration routes *in vivo* other than intratumoral injection. The state of the art for gene therapy was unpredictable at the time of the invention. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. One of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time". The fate of the DNA vector itself, the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, and the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced are all important factors for a successful gene therapy. In vitro data can not be extrapolated to the success *in vivo* for gene therapy. Each gene therapy case has to be considered independently. The claimed methods are not routine experimentations and require undue experimentation to practice over the full scope of the invention claimed.

Applicants argue that the present invention overcome the problems in gene therapy in vivo reported by Deonarain and Verma and the tumor-specific promoter of the present invention would ensure high copy number of vectors in a small treatment area, and high-level or long-term expression is unnecessary because expression of only a relatively small amount of toxin is required (amendment, p. 6-7). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 12-18-02 (Paper No. 7) and the reasons set forth above.

Claim Rejections - 35 USC § 102

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless -
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1-4, 15 and 18 remain rejected under 35 U.S.C. 102(b) as being anticipated by Mathupala et al., 1995 (The Journal of Biological Chemistry, Vol. 270, No. 28, p. 16918-16925, IDS-CA) and is repeated for the reasons set forth in the preceding Official action mailed 12-18-02 (Paper No. 7). Applicant's arguments filed 4-23-03 have been fully considered but they are not persuasive.

Applicants argue that Mathupala does not teach that the rat Hex II promoter is tumor specific and the rat Hex II promoter is selectively activated in tumor cells in general, and the tumor specific activity would be expected in species other than rat (amendment, p. 8). This is not

found persuasive because of the reasons set forth in the preceding Official action mailed 12-18-02 (Paper No. 7). The claims recite the rat Hex II promoter is selectively activated in tumor cells as compared to normal cells but does not require the rat Hex II promoter has to have tumor specific activity in species other than rat. Mathupala teaches higher level of type II hexokinase expression in AS-30D hepatoma cell line as compared to normal cells, and isolated and identified the sequence of the 4.3 kb promoter of type II hexokinase (Hex II promoter) from rat. Thus, the rat Hex II promoter is selectively activated in rat tumor cells as compared to rat normal cells. Tumor cells encompass rat tumor cells and normal cells encompass rat normal cells. The teaching of Mathupala indicates that the rat Hex II promoter activity is tumor-specific in rat. Further, claims 1-4, 15 and 18 are product claims and the promoter sequence disclosed by Mathupala is a rat Hex II promoter, thus, it is inherent to said rat Hex II promoter to be tumor-specific. Therefore, claims 1-4, 15 and 18 are anticipated by Mathupala.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. Claims 1-6, 8-20 and 23-25 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Mathupala et al., 1995 (The Journal of Biological Chemistry, Vol. 270, No. 28, p. 16918-

16925, IDS-CA) in view of Stratford-Perricaudet et al., 1992 (IDS-CI), Osawa et al., 1996 (IDS-CE) and Martuza et al., US Patent No. 5,728,379 (IDS-AA) and further in view of Adams et al., 1995 (IDS-CB) and is repeated for the reasons set forth in the preceding Official action mailed 12-18-02 (Paper No. 7). Applicant's arguments filed 4-23-03 have been fully considered but they are not persuasive.

Applicants argue that Mathupala does not teach that rat Hex II promoter is tumor-specific and does not suggest similar Hex II gene expression in cells other than rat cells. Applicants further argue that the specification discloses tumor-specific activity of the rat Hex II promoter both in human and murine cells, which is unexpected result (amendment, p. 9-10). This is not found persuasive because of the reasons set forth in the preceding Official action mailed 12-18-02 (Paper No. 7) and the reasons set forth above under 35 U.S.C. 102(b) rejection. Mathupala teaches higher level of type II hexokinase expression in AS-30D hepatoma cell line as compared to normal cells, and Adams teaches increased hexokinase II expression in rat tumor cells such as hepatoma cells than in the rat normal counterpart, and also teaches increased hexokinase II expression in human renal carcinoma cells than in the human normal counterpart. Thus, it would have been obvious for one of ordinary skill at the time of the invention that the Hex II promoter is tumor-specific in both human cells and murine cells.

Conclusion

No claim is allowed.

7. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (703) 305-1678. The examiner can normally be reached on Monday to Friday from 9 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on (703) 305-4051. The fax phone number for this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist, whose telephone number is (703) 308-0196.

S Chen